IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Scheller, D. *et al.*
Serial No.:	**10/587,637**
Filed:	February 6, 2007
Title:	(S)-2-N-PROPYLAMINO-5-HYDROXYTETRALIN AS A D3 AGONIST
Group Art Unit:	1628
Examiner:	C.D. Ricci
Confirmation No.:	2828
Docket No.:	**6102-000034/US/NP**
Client Ref.:	P/Sche/III/7/03

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28 January 2011

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

This paper and its attachments are filed in support of Applicant's Notice of Appeal to the Board of Patent Appeals and Interferences (the Board) from a decision of the U.S. Patent Office. The entire record of the current Application is incorporated herein by reference.

The two months shortened statutory period following the 6 December 2010 filing of the Notice of Appeal expires 6 February 2011. Appellant's brief in support of the Notice of Appeal is believed timely under 37 C.F.R. § 41.37(a)(1). Authorization is provided to charge the fee for filing a brief in support of the Notice of Appeal under 37 C.F.R. § 41.20(b)(2). No additional fees are believed required in connection with this Appeal Brief. However, the Commissioner is authorized to charge any underpayment or credit any overpayment of fees to Deposit Account No. **08-0750**.

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(A) REAL PARTY IN INTEREST (37 C.F.R. 41.37(c)(1)(i))

The real party in interest in the present Appeal is SRZ Properties, Inc., the Assignee of record in Application Serial No. 10/587,637, having a place of business in Wilmington, Delaware, USA and a correspondence address of 103 Foulk Road Suite 254, Wilmington, Delaware 19803-3742. SRZ Properties, Inc. is the owner of the entire right, title and interest in the current Application by virtue of an Assignment recorded 04 March 2009, at reel 022341, frame 0995.

(B) RELATED APPEALS AND INTERFERENCES (37 C.F.R. 41.37(c)(1)(ii))

Appellant knows of no other current appeals or interferences which will directly affect or be directly affected by or which have a bearing on the Board's decision in the present Appeal.

(C) STATUS OF CLAIMS (37 C.F.R. 41.37(c)(1)(iii))

Claims 10-14, 19 and 20 stand rejected in the current Application and are the subject of this appeal.

Claims 15–18 are pending but presently withdrawn.

Claims 1-9 and 21 were previously canceled.

(D) STATUS OF AMENDMENTS (37 C.F.R. 41.37(c)(1)(iv))

No amendment was filed subsequent to final rejection. Pending Claims 10-14, 19 and 20 correspond to those submitted on 29 June 2009 in the Request for Continued Examination and Response to Office Action.

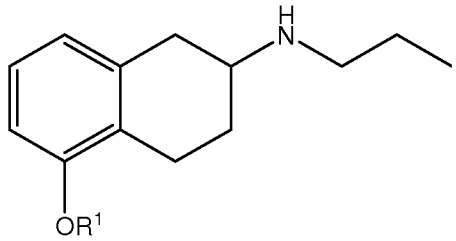
In the Final Office Action of 07 June 2010, the Examiner notes that the "amendments filed 3/01/2010 were entered." However, Appellant's response filed 1 March 2010 did not include amendments. As stated above, the claims were last amended in the Request for Continued Examination and Response to Office Action submitted on 29 June 2009.

A copy of the pending claims is included in the Claims Appendix attached hereto in accordance with 37 C.F.R. 41.37(c)(1)(viii), Section (H).

(E) SUMMARY OF CLAIMED SUBJECT MATTER (37 C.F.R. 41.37(c)(1)(v))

All paragraph references in this section relate to the current Application (Serial No. 10/587,637) as filed on 06 February 2007.

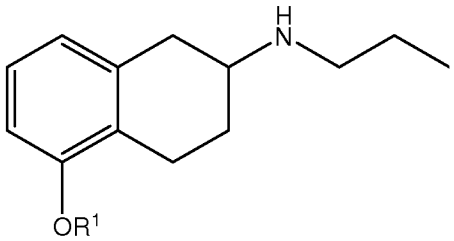
Independent Claim 10 is drawn to a pharmaceutical composition comprising (S)-2-N-propylamino-5–hydroxytetralin or a pharmaceutically acceptable salt or prodrug thereof, and at least one pharmaceutically acceptable carrier or adjuvant. The prodrug is of the formula



or a salt thereof. R^1 is selected from the group consisting of acyl, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, acetal, ketal, $–C(O)NR^2R^3$, $–C(O)NHR^2$, $-P(O_2H)OR^2$ and $–P(O_2H)R^2$, wherein R^2 and R^3 are independently selected from H, $C_{1–6}$ alkyl, $C_{3–10}$ cycloalkyl, benzyl and phenyl. The at least one pharmaceutically acceptable carrier or adjuvant is selected from the group consisting of fillers, disintegrants, binders, lubricants, stabilizers, flavors, antioxidants, preservatives, dispersants, buffers and electrolytes. Claim 10 is generally supported throughout the specification, for example at paragraph **[0024]** ((S)-2-N-propylamino-5-hydroxytetralin or a pharmaceutically acceptable salt or prodrug thereof) and paragraph **[0034]** (prodrug or salt thereof), in conjunction with paragraphs **[0026]** (pharmaceutically acceptable salts), **[0058]** (pharmaceutical compositions comprising salts and prodrugs thereof and pharmaceutical carriers or adjuvants) and **[0060]** (suitable pharmaceutical carriers or adjuvants).

Claims 11-14 ultimately depend from Claim 10 and embody all limitations of Claim 10.

Independent Claim 19 is drawn to a compound having the formula



or a salt thereof. R^1 is selected from the group consisting of acyl, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, acetal, ketal, $-C(O)NR^2R^3$, $-C(O)NHR^2$, $-P(O_2H)OR^2$ and $-P(O_2H)R^2$, wherein R^2 and R^3 are independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, benzyl and phenyl. The compound is in the (S)-configuration, and when administered to a human body, the compound is cleaved, processed or metabolized to (S)-2-N-propylamino-5-hydroxytetralin. Claim 19 is generally supported throughout the specification, for example at paragraph **[0034]** (prodrug or salt thereof), in conjunction with paragraphs **[0026]** (pharmaceutically acceptable salts), and **[0027]** (defining prodrug of (S)-2-N-propylamino-5-hydroxytetralin).

Claim 20 ultimately depends from claim 19 and embodies all limitations of claim 19.

(F) GROUNDS OF REJECTION TO BE REVIEWED IN APPEAL (37 C.F.R. 41.37(c)(1)(vi))

1. Rejection of Claims 19-20 under 35 U.S.C. §103(a) over van Vliet *et al.* (1996) J. Med Chem., 39:4233-4237 (hereinafter van Vliet) in view of Wikström *et al.* (1985) J. Med. Chem., 28:215-225 (hereinafter Wikström) and Rodenhuis (2000) Dissertation, Rijksuniversiteit Groningen titled "New, centrally acting dopaminergic agents with an improved oral bioavailability: synthesis and pharmacological evaluation" (hereinafter Rodenhuis).

2. Rejection of Claims 10-14 under 35 U.S.C. §103(a) over van Vliet in view of Wikström and Rodenhuis, and in further view of den Daas *et al.* (1990) Nauyn-Schmiedeberg's Arch. Pharmacol., 343:655-659 (hereinafter den Daas).

(G) ARGUMENT (37 C.F.R. 41.37(c)(1)(vii))

1. Summary of Facts

Appellant stipulates to the following facts:

A. van Vliet, the primary reference, does not disclose, teach or suggest (S)-2-N-propylamino-5-hydroxytetralin.

B. Wikström and Rodenhuis, the secondary references, do not disclose 2-N-propylamino-5-hydroxytetralin, nor (S)-2-N-propylamino-5-hydroxytetralin.

C. At the time of the invention, $\mathbf{D_3}$ selectivity was considered a promising target for the development of active agents for the treatment of different psychiatric and motor diseases. *See* the specification as filed at paragraphs **[0002]** and **[0003]**.

D. (S)-2-N-propylamino-5-hydroxytetralin is highly selective for $\mathbf{D_3}$ and is a pure $\mathbf{D_3}$ agonist.

E. "One of ordinary skill in the art looking for a compound selective for D3 – would not have selected [racemic]-2-N-propylamino-5-hydroxytetralin from the 27 compounds tested in van Vliet..." *See* Final Office Action, at p. 6.

F. van Vliet does not disclose functional data, and thus, does not report on the agonist or antagonist activity of the tested compounds.

G. Although Wikström reports on enantiomeric separation of 5-OH-DPAT, a N,N-dialkylatated compound, 5-OH-DPAT is functionally different than a N-dealkylated compound, like 2-N-propylamino-5-hydroxytetralin.

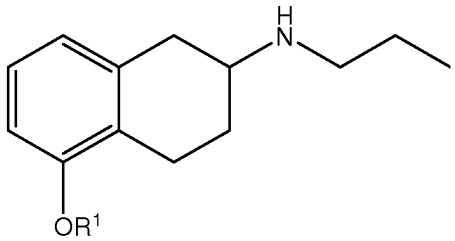
H. AJ76, the structurally closest compound in the art of record, has reduced $\mathbf{D_3}$ selectivity and is a pure antagonist. AJ76 is opposite acting to (S)-2-N-propylamino-5-hydroxytetralin.

2. Rejection Under 35 U.S.C. §103(a) Over van Vliet in View of Wikström and Rodenhuis

2.1 Claim 19

Claims 19–20 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over van Vliet in view of Wikström and Rodenhuis. Withdrawal or reversal of this rejection is sought by the present Appeal.

Claim 19 is drawn to a compound having the formula



or a salt thereof, wherein the compound is in the (S)-configuration, and wherein when administered to a human body, the compound is cleaved, processed, or metabolized to (S)-2-N-propylamino-5-hydroxytetralin. For at least the reasons set forth below, the Final Office Action fails to establish a presumption of *prima facie* obviousness. Further, even if a presumption of *prima facie* obviousness of Claim 19 had been established (which is not admitted herein), Appellant provides sufficient rebuttal evidence to overcome any presumption of *prima facie* obviousness.

2.1.1. No Pattern of Preference to (1) Select Racemic 2-N-propylamino-5-hydroxytetralin, (2) Select the (S)-Enantiomer of 2-N-propylamino-5-hydroxytetralin, and (3) Select a Prodrug of the (S)-Enantiomer

The Final Office Action (p. 6) admits that "one of ordinary skill in the art – looking for a compound selective for D_3 – would not have selected 2-N-propylamino-5-hydroxytetralin from the 27 compounds tested in *van Vliet et al*…" But then notes that "it is still the case that one of ordinary skill in the art – looking for a compound selective for D_{2L} ***and*** D_3 – **would** have selected 2-N-propylamino-5-hydroxytetralin from the 27 compounds tested in *van Vliet et al.*" The Examiner concludes (p.8) that "the reason or motivation to modify a reference to arrive at the claimed invention can be for different purpose or to solve a different problem." The Examiner, in other words, uses the alleged selectivity for $\mathbf{D_{2L}}$ and $\mathbf{D_3}$ of 2-N-propylamino-5-hydroxytetralin as motivation in van Vliet to pick out 2-N-propylamino-5-hydroxytetralin. This is improper motivation.

One of ordinary skill in the art would have been motivated to select compounds that are $\mathbf{D_3}$ selective. At the time of the invention, $\mathbf{D_3}$ selectivity was considered a promising target for the development of active agents for the treatment of different psychiatric and motor diseases. *See* the specification as filed at paragraphs **[0002]** and **[0003]**. Accordingly, one of

ordinary skill in the art was looking for a compound highly selective for $\mathbf{D_3}$, not a compound selective for $\mathbf{D_{2L}}$ and $\mathbf{D_3}$. Thus, 2-N-propylamino-5-hydroxytetralin having alleged $\mathbf{D_{2L}}$ and $\mathbf{D_3}$ selectivity would not have provided motivation to one of ordinary skill in the art to select 2-N-propylamino-5-hydroxytetralin. Accordingly, as admitted by the Examiner, one of ordinary skill in the art looking for a compound with pronounced $\mathbf{D_3}$ selectivity - would not have had any reason to select 2-N-propylamino-5-hydroxytetralin from the 27 compounds tested in van Vliet.

The evidence of record, including Hacksell and Swart, further support that the art "as a whole" provides no motivation to select 2-N-propylamino-5-hydroxytetralin. *See* Hacksell *et al.* (1979) J. Med. Chem. 22(12):1469–1475 ("Hacksell") ("the agonistic activity of [racemic 2-N-propylamino-5-hydroxytetralin] with an ED_{50} of 40 nM/kg is only moderate and the AUC and the half life are short in comparison to the other evaluated compounds."); *see also* Swart *et al.* (1993) Toxicol. Meth. 3:279–290, at 279 (describing 2-N-propylamino-5-hydroxytetralin as a rotigotine metabolite with weaker dopaminergic activity and concludes that the N-dealkylated metabolites have a dopaminergic activity too weak for them to have therapeutic effects). In response, the Examiner (p. 6) dismisses Hacksell as not "teaching away" from 2-N-propylamino-5-hydroxytetralin. Regardless of "teaching away", the Final Office Action does not address that Hacksell, congruent with the art as a whole, demotivates selection of 2-N-propylamino-5-hydroxytetralin. Furthermore, in response to Swart, the Examiner concludes that "while Swart et al indicate that 2-N-propylamino-5-hydroxytetralin does not bind dopaminergic receptors as efficiently as N-0437, *Swart et al* do not overcome the data clearly demonstrating that 2-N-propylamino-5-hydroxytetralin possesses significant dopamine agonistic activity." *See* Final Office Action, at p. 6. However, as discussed above, and admitted by the Examiner, the data in van Vliet (which is what Appellant assumes is meant by "data"), at most, provides insight into selectivity for $\mathbf{D_{2L}}$ and $\mathbf{D_3}$ and van Vliet does not report functional data (*i.e.* agonist or antagonist activity). Thus, van Vliet does not demonstrate that 2-N-propylamino-5-hydroxytetralin possesses pronounced "D_3 selectivity" or "significant dopamine agonistic activity" and does not overcome Swart's opinion that 2-N-propylamino-5-hydroxytetralin is weak. Accordingly, Swart and Hacksell provide further

support that one of ordinary skill in the art would not have been motivated to select 2-N-propylamino-5-hydroxytetralin.

Furthermore, Wikström and Rodenhuis do not provide any motivation to select 2-N-propylamino-5-hydroxytetralin, as neither of these documents disclose, teach or suggest 2-N-propylamino-5-hydroxytetralin. In response, the Examiner (p. 7) states that "the secondary references are applied to demonstrate why one of ordinary skill in the art…would have been motivated to subject the compound to enantiomeric separation and formulate prodrugs thereof." However, without any motivation to select 2-N-propylamino-5-hydroxytetralin, how could the secondary references provide motivation to perform enantiomeric separation or formulation of prodrugs of 2-N-propylamino-5-hydroxytetralin? Instead, from Wikström and Rodenhuis, one would have to:

(1) find a compound which is highly selective for $\mathbf{D_3}$;

(2) find a compound that is also an agonist;

(3) then obtain the enantiomers;

(4) test the enantiomers; and

(5) prepare specific pro-drugs.

The five steps would have to be performed without a pattern of preference for selection of even 2-N-propylamino-5-hydroxytetralin from van Vliet, Wikström or Rodenhuis. With no guidance to select 2-N-propylamino-5-hydroxytetralin, there is no guidance in the secondary documents for performing enantioseparation per Wikström to provide the (S)-enantiomer or preparing prodrugs of the (S)-enantiomer per Rodenhuis.

2.1.2 One of Ordinary Skill in the Art Could Not Have Predicted Two Properties: High $\mathbf{D_3}$ Selectivity and Pure Agonist Activity

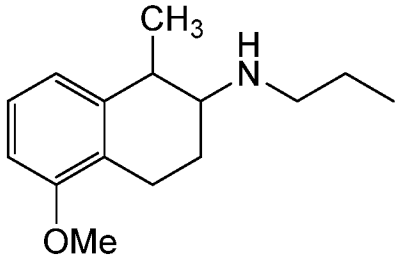
Even if, *arguendo*, motivation existed to select racemic 2-N-propylamino-5-hydroxytetralin from van Vliet for enantiomeric separation (per Wikström) and prodrug formulation (per Rodenhuis), the predictability of outcome or reasonable expectation of success required to establish a presumption of *prima facie* obviousness is lacking.

(a) **No Data for Claimed Compound, (S)-2-N-propylamino-5-hydroxytetralin:** There is no disclosure, much less data for (S)-2-N-propylamino-5-hydroxytetralin in the cited art. Appellant is the first to discover that (S)-2-N-propylamino-5-hydroxytetralin has two unpredictable properties: (1) high $\mathbf{D_3}$ selectivity; and (2) pure agonist activity.

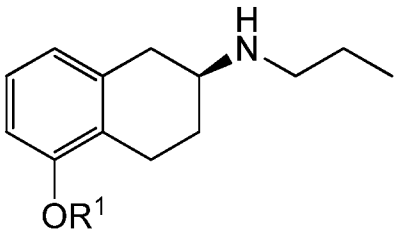
(b) **No Predictability of D_3 Selectivity:** The Examiner alleges that van Vliet reports that 2-N-propylamino-5-hydroxytetralin is a potent $\mathbf{D_{2L}/D_3}$ receptor agonist and citing *In re Papesch,* states that "the D_3 selectivity of the *prima facie* obvious compound motivated by the prior art (for arguable different reasons) is merely a property or result of said compound. For this reason, whether someone of skill in the art would have predicted that the *prima facie* obvious compound would possess D_3 selectively is not relevant for determining obviousness as asserted by Applicant." *See* Final Office Action, p. 8. This is an improper conclusion. *In re Papesch* teaches that it is an error of law to fail to take into consideration the biological or pharmaceutical property of a compound. 137 U.S.P.Q. 43, at 51; *see also Eli Lilly and Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369 (Fed. Cir. 2006) (further reiterating that it "will not ignore a relevant property of a compound in the obviousness calculus."). Accordingly, even if true that van Vliet reports that the racemate 2-N-propylamino-5-hydroxytetralin is a potent $\mathbf{D_{2L}/D_3}$ compound, (S)-2-N-propylamino-5-hydroxytetralin's selectivity for $\mathbf{D_3}$ is a unique property that could not be predicted from the cited art and should be considered in an obviousness determination.

(c) **No Disclosure and No Predictability of Pure Agonist Activity:** The Examiner fails to provide any support in the cited art for a teaching that 2-N-propylamino-5-hydroxytetralin, much less (S)-2-N-propylamino-5-hydroxytetralin, would have pure agonistic activity (the second unpredictable property). van Vliet does not report any functional tests. Therefore, one cannot determine from van Vliet whether compound 11 (2-N-propylamino-5-hydroxytetralin) is an antagonist or agonist, let alone a pure agonist. Therefore, it is erroneous to conclude that van Vliet teaches that the racemate is a "potent D_{2L}/D_3 receptor agonist", much less that it provides any prediction to one of ordinary skill in the art that (S)-2-N-propylamino-5-hydroxytetralin is a pure $\mathbf{D_3}$ agonist.

(d) **Closest Structurally-Related Compound, AJ76, Has Opposite Properties:** Not only are the two properties (high D_3 selectivity and pure agonist activity) unpredictable in light of van Vliet and the cited secondary references, AJ76 is the closest-structurally related compound to a prodrug of S-2-N-propylamino-5-hydroxytetralin as claimed in Claim 19, and AJ76 is opposite acting.



vs



AJ76 **Claim 19 S-prodrug**

> Structurally related AJ76 is described as a **pure antagonist**, and thus, "[t]he resulting therapeutic profile of (S)-2-N-propylamino-5-hydroxytetralin differs considerably from that of the structurally similar AJ76." *See* the specification as filed at paragraph **[0021]**. Therefore, Appellant submits that even if one of ordinary skill in the art would have been motivated to select racemic 2-N-propylamino-5-hydroxytetralin for resolution, one of ordinary skill in the art based on the closest-structurally related compound to the claimed prodrug would have predicted at most, a pure antagonist compound. Thus, the fact that (S)-2-N-propylamino-5-hydroxytetralin shows **purely agonistic** activity could not have been predicted by one of ordinary skill in the art.

In response to Appellant's evidence, the Examiner states that "the skilled artisan would have reasonably predicted that enantiomeric separation of 2-N-propylamino-5-hydroxytetralin and prodrug formulation would provide a compound having the same and/or better results in view of *Wikstrom et al* and *Rodenhuis*." *See* Final Office Action, p. 7. The Examiner cites *In re Deuel,* 51 F.3d 1552 (Fed. Cir. 1995), and alleges that Wikström teaches "enantiomeric separation of the structurally and functionally related compound 5-OH-DPAT and, based on their structural and functional relationship, one of ordinary skill in the art would have reasonably predicted enantiomeric separation of 2-N-propylamino-5-hydroxytetralin would also provide compounds having the same and/or better activity [as 5-OH-DPAT]." *See* Final Office Action, p. 7 bridging p. 8. This is an improper conclusion: **5-OH-DPAT, a N,N-dialkylated compound, is recognized in the art as functionally different from N-dealkylated compounds.**

It is true that *In re Deuel* stands for the proposition that a known compound may suggest its analogs or isomers. However, *In re Deuel* does not stand for the proposition that a compound is obvious if a functionally different compound is known in the art. The evidence

of record establishes that the art clearly distinguishes N,N-dialkylated compounds (*i.e.* 5-OH-DPAT) from the N-dealkylated compounds (*i.e.* racemic 2-N-propylamino-5-hydroxytetralin). Specifically Swart sets forth

> [t]he N-dealkylated metabolites showed weak affinities in dopaminergic receptor-binding studies, whereas the catechol has an affinity comparable to the parent compound. However, because of the high further metabolic conversion in intact organs as well as *in vivo,* it seems unlikely that the catechol metabolite can contribute to the therapeutic efficacy of the parent drug. This possibility is <u>even lower</u> for the N-dealkylated metabolites because of their <u>low receptor affinities.</u>

See e.g. Swart *et al.* (1993) <u>Toxicol. Meth.</u> 3:279–290, at 289 (emphasis added). Therefore, the art has established a difference between these compounds even if they are structurally similar – *i.e.* the art suggests that one of ordinary skill in the art cannot make any prediction of N-dealkylated compounds from N,N-dialkylated compounds. Additionally, van Vliet reports that 5-OH-DPAT was not selective for $\mathbf{D_3}$ over $\mathbf{D_2}$. Conversely, (S)-2-N-propylamino-5-hydroxytetralin is selective for $\mathbf{D_3}$. Accordingly, (S)-2-N-propylamino-5-hydroxytetralin and 5-OH-DPAT, are recognized in the art as functionally different. Thus, because the compounds are recognized as functionally different, one of ordinary skill in the art could <u>not</u> have predicted success in enantiomeric separation of an N-dealkylated compound (*i.e.* 2-N-propylamino-5-hydroxytetralin) from a N,N-dialkylated compound (*i.e.* 5-OH-DPAT).

Thus, with (1) no disclosure or data on (S)-2-N-propylamino-5-hydroxytetralin in the cited art; and (2) 2-N-propylamino-5-hydroxytetralin not being highly selective for $\mathbf{D_3}$; and (3) no disclosure of functional tests in the cited art, much less a teaching that 2-N-propylamino-5-hydroxytetralin has pure agonistic activity; and (4) the structurally related AJ76 having the opposite activity, *i.e.* AJ76 is a pure antagonist, and (5) the art clearly distinguishing N,N-dialkylated compounds (*i.e.* 5-OH-DPAT) from the N-dealkylated compounds, one of ordinary skill in the art could not have predicted two properties of (S)-2-N-propylamino-5-hydroxytetralin: high $\mathbf{D_3}$ selectivity and pure agonist activity. Appellant submits no presumption of *prima facie* case obviousness has been established for Claim 19 over van Vliet, Wikström and Rodenhuis.

2.1.3. Rebuttal Evidence: Unexpected Results

Even if a presumption of *prima facie* obviousness of Claim 19 had been established (which is not admitted herein), the Final Office Action (p. 8) states "a showing that the *prima facie* obvious compound possesses these unexpected properties could be considered evidence of **unexpected results** to overcome a rejection based on obviousness." (S)-2-N-propylamino-5-hydroxytetralin possesses two unexpected properties: pronounced $\mathbf{D_3}$ selectivity and pure agonistic activity.

(a) **(S)-2-N-propylamino-5-hydroxytetralin Has Two Unexpected Properties: High D_3 Selectivity and Pure Agonist Activity.**

Claim 19 recites a *Markush* group of prodrugs. Unlike 2-N-propylamino-5-hydroxytetralin, AJ76 is a methyl ester prodrug (see section above). Accordingly, one of ordinary skill in the art would naturally start with a compound such as AJ76. AJ76, however, demonstrated a reduced $\mathbf{D_3}$ preference. *See* the specification as filed, at paragraph **[0021]**. Additionally, AJ76 is a pure antagonist. *See* the specification as filed, at paragraph **[0021]**. Accordingly, one of ordinary skill in the art would expect, at most, that a prodrug of (S)-2-N-propylamino-5-hydroxytetralin would demonstrate reduced $\mathbf{D_3}$ preference and be a pure antagonist like AJ76.

First, Appellant unexpectedly discovered that (S)-2-N-propylamino-5-hydroxytetralin has strongly pronounced functional $\mathbf{D_3}$ selectivity in comparison to the $\mathbf{D_1}$ receptor as well as significant selectivity in comparison to the $\mathbf{D_2}$ receptor. *See* the specification as filed, at paragraph **[0020]**. (S)-2-N-propylamino-5-hydroxytetralin's pronounced $\mathbf{D_3}$ selectivity is different than the structurally similar compound AJ76. This unexpected property is enough to overcome any presumption of *prima facie* obviousness.

Second, Appellant, for the first time, established that (S)-2-N-propylamino-5-hydroxytetralin has pure agonist activity. Nothing in the cited art discloses, much less provides functional data on (S)-2-N-propylamino-5-hydroxytetralin. Specifically, van Vliet fails to disclose any functional tests used to determine antagonist and/or agonist levels. Moreover, the structurally very similar AJ76 was identified as a pure antagonist, making the pure agonist activity of (S)-2-N-propylamino-5-hydroxytetralin unexpected. *See* specification

as filed at paragraph **[0021]**.

(b) **Claim 19 Is Commensurate In Scope With the Unexpected Properties.**

The Examiner reminds Appellant "that the claims must be drafted commensurate in scope with the unexpected results" and alleges that "the claims appear to be broader than the alleged unexpected results." *See* Final Office Action, at p. 9. The above unexpected results are directed to data set forth in the specification for (S)-2-N-propylamino-5-hydroxytetralin. Claim 19 recites a *Markush* group of prodrugs that when administered to the human body each is cleaved, processed or metabolized to (S)-2-N-propylamino-5-hydroxytetralin (an element of the claim). The resulting unexpected therapeutic profile of (S)-2-N-propylamino-5-hydroxytetralin, *i.e.* high $\mathbf{D_3}$ selectivity and pure agonist activity, is what Appellant asserts as evidence of unexpected results. Thus, the unexpected properties are commensurate in scope with Claim 19.

For the aforementioned reasons, a presumption of *prima facie* obviousness has not been established for Claim 19, and even if the Board determines a presumption exists, the evidence of unexpected results properly rebuts any such presumption.

Withdrawal or reversal of this rejection is sought by the present Appeal.

2.2. Claim 20

Claim 20 depends from Claim 19 and therefore embodies all limitations of Claim 19. For all the reasons set forth above, the Examiner has failed to establish a presumption of *prima facie* obviousness of Claim 19 over van Vliet in view of Wikström and Rodenhuis. Furthermore, if a presumption of *prima facie* obviousness of Claim 19 exists (which is not admitted herein), the presumption is rebutted for the reasons set forth in Section 2.1.3. Claim 20 is patentable over van Vliet in view of Wikström and Rodenhuis for at least the same reasons as Claim 19. If an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. MPEP 2143.03.

Withdrawal or reversal of this rejection is sought by the present Appeal.

3. Rejection Under 35 U.S.C. §103(a) Over van Vliet in View of Wikström and Rodenhuis, and In Further View of den Daas

Claims 10-14 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over van Vliet in view of Wikström and Rodenhuis in further view of den Daas. Withdrawal or reversal of this rejection is sought by the present Appeal.

3.1 Claim 10

At the outset, the Final Office Action (p. 11) states "Applicant does not traverse the rejection of claims 10-14 beyond those arguments already discussed." However, Appellant did specifically respond to the rejection of Claims 10-14 in the 1 March 2010 response. *See* 1 March 2010 Response, at p. 8-9.

Claim 10 is drawn to a composition containing (S)-2-N-propylamino-5-hydroxytetralin or a pharmaceutically acceptable salt or prodrug thereof and at least one pharmaceutically acceptable carrier or adjuvant. Claim 10 is rejected on similar grounds to Claim 19, with the further argument that den Daas reports "compositions comprising structurally and functionally related compounds and further comprising a pharmaceutically acceptable carrier or adjuvant, wherein the composition is adapted for transdermal, transmucosal, or parenteral administration." *See* Final Office Action, p. 11. However, den Daas reports "[f]or transdermal application the HCl salts were converted into the free bases and dissolved in an alcohol and polyethyleneglycol-400 mixture (6:4). All ester prodrugs proved to be stable in the solvents used for the experiments." *See* den Daas, at p. 656.

Even if the Examiner's assertions regarding den Daas were true (which is not admitted herein), this does not cure the deficiencies of van Vliet in view of Wikström and Rodenhuis, as it still does not provide any motivation for selecting 2-N-propylamino-5-hydroxytetralin, much less the (S)-enantiomer; or provide any reasonable expectation of success that the S-enantiomer would achieve successful results. Furthermore, there is nothing in den Daas that defeats Appellant's rebuttal evidence set forth in Section 2.1.3 above (incorporated herein). Claim 10, although of different scope, is therefore nonobvious for at least the same reasons that Claim 19 is nonobvious.

Withdrawal or reversal of this rejection is sought by the present Appeal.

3.2 Claims 11-14

Claims 11-14 depend from Claim 10 and therefore embody all limitations of Claim 10. For all the reasons set forth above, the Examiner has failed to establish a presumption of *prima facie* obviousness of Claim 10 over van Vliet in view of Wikström and Rodenhuis, and in further view of den Daas. Therefore all claims dependent therefrom, including Claims 11-14, are patentable over van Vliet in view of Wikström and Rodenhuis, and in further view of den Daas for at least the same reasons as Claim 10.

Withdrawal or reversal of this rejection is sought by the present Appeal.

Respectfully submitted,

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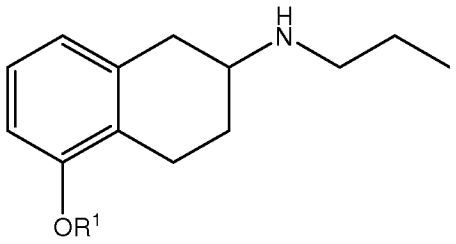
(H) CLAIMS APPENDIX (37 C.F.R. 41.37(c)(1)(viii))

1.–9. (Canceled)

10. (Previously presented) A pharmaceutical composition comprising (S)-2-N-propylamino-5-hydroxytetralin or a pharmaceutically acceptable salt or prodrug thereof, and at least one pharmaceutically acceptable carrier or adjuvant, wherein the prodrug is of the formula



or a salt thereof;

wherein R^1 is selected from the group consisting of acyl, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, acetal, ketal, $–C(O)NR^2R^3$, $–C(O)NHR^2$, $-P(O_2H)OR^2$ and $–P(O_2H)R^2$, wherein R^2 and R^3 are independently selected from H, $C_{1–6}$ alkyl, $C_{3–10}$ cycloalkyl, benzyl and phenyl and

wherein the at least one pharmaceutically acceptable carrier or adjuvant is selected from the group consisting of fillers, disintegrants, binders, lubricants, stabilizers, flavors, antioxidants, preservatives, dispersants, buffers and electrolytes.

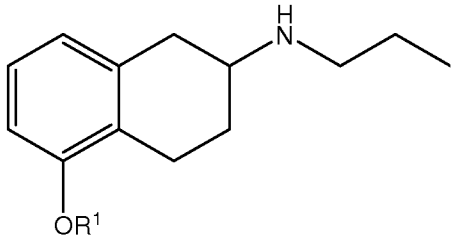
11. (Previously presented) The composition of Claim 10, comprising (S)-2-N-propylamino-5-hydroxytetralin or a pharmaceutically acceptable salt thereof.

12. (Previously presented) The composition of Claim 10, comprising a prodrug or a salt thereof wherein R^1 is selected from $C_{1–6}$ alkylcarbonyl, $C_{3–10}$ cycloalkylcarbonyl, benzoyl, $–C(O)NR^2R^3$ and $–C(O)NHR^2$.

13. (Previously presented) The composition of Claim 10, that is adapted for transdermal, transmucosal or parenteral administration.

14. (Previously presented) The composition of Claim 10, wherein the (S)-2-N-propylamino-5-hydroxytetralin or salt or prodrug thereof is present as a pure (S)-enantiomer.

15. (Withdrawn) A method for treatment or prophylaxis of a disease or for ablactation in a subject, comprising administering to the subject (S)-2-N-propylamino-5-hydroxytetralin or a pharmaceutically acceptable salt or prodrug thereof, wherein the prodrug is of the general formula



wherein R^1 is selected from the group consisting of acyl, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, acetal, ketal, $-C(O)NR^2R^3$, $-C(O)NHR^2$, $-P(O_2H)OR^2$ and $-P(O_2H)R^2$, wherein R^2 and R^3 are independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, benzyl and phenyl, or a salt thereof; and

wherein the disease is selected from the group consisting of depressions, anxiety disorders, sexual dysfunctions, galactorrhea, acromegaly, glaucoma, cognitive disorders, restless leg syndrome, attention deficit hyperactivity syndrome (ADHS), hyperprolactinemia, hyperprolactinoma, eating disorders, dopa-sensitive dyskinesias, Parkinson-associated movement disorders, dopa- and neuroleptic-induced movement disorders, cocaine, alcohol, opiate and nicotine addictions, and neurodegenerative disorders.

16. (Withdrawn) The method of Claim 15, wherein the disease is selected from the group consisting of restless leg syndrome, L-dopa-sensitive dyskinesias, Parkinson-associated movement disorders, L-dopa- and neuroleptic-induced movement disorders, and cocaine, alcohol, opiate and nicotine addictions.

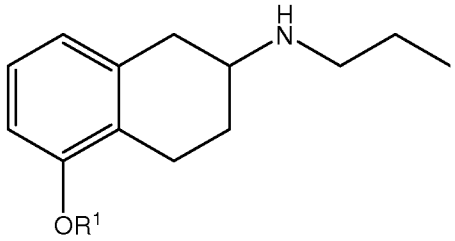
17. (Withdrawn) The method of Claim 15, wherein the disease is a movement disorder which is

(a) morbus Parkinson associated,

(b) induced by L-dopa, or

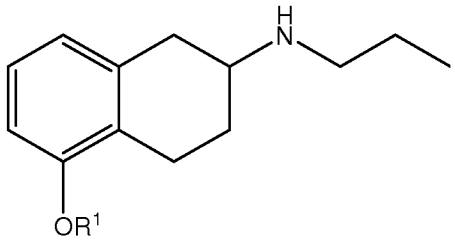
(c) induced by a neuroleptic.

18. (Withdrawn) A method for treating a disease that responds to therapy by dopamine or dopamine agonists, comprising administering to a subject having the disease (S)-2-N-propylamino-5-hydroxytetralin or a pharmaceutically acceptable salt or prodrug thereof, wherein the prodrug is of the general formula



wherein R^1 is selected from the group consisting of acyl, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, acetal, ketal, $-C(O)NR^2R^3$, $-C(O)NHR^2$, $-P(O_2H)OR^2$ and $-P(O_2H)R^2$, wherein R^2 and R^3 are independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, benzyl and phenyl, or a salt thereof.

19. (Previously presented) A compound having the formula



or a salt thereof;

wherein R^1 is selected from the group consisting of acyl, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, acetal, ketal, $-C(O)NR^2R^3$, $-C(O)NHR^2$, $-P(O_2H)OR^2$ and $-P(O_2H)R^2$, wherein R^2 and R^3 are independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, benzyl and phenyl;

said compound being in the (S)-configuration; and

wherein said compound, when administered to a human body, is cleaved, processed or metabolized to (S)-2-N-propylamino-5-hydroxytetralin.

20. (Previously presented) The compound of Claim 19, wherein R^1 is selected from C_{1-6} alkylcarbonyl, C_{3-10} cycloalkylcarbonyl, benzoyl, $-C(O)NR^2R^3$ and $-C(O)NHR^2$.

21. (Canceled)

(I) EVIDENCE APPENDIX (37 C.F.R. 41.37(c)(1)(ix))

1. van Vliet *et al.* (1996) J. Med Chem., 39:42333-4237. This evidence was entered into the record by the Appellant in the Information Disclosure Statement dated 15 April 2008.

2. Wikström *et al.* (1985) J. Med. Chem., 28:215-225. This evidence was entered into the record by the Appellant in the Information Disclosure Statement dated 15 April 2008.

3. Rodenhuis (2000) Dissertation, Rijksuniversiteit Groningen titled "New, centrally acting dopaminergic agents with an improved oral bioavailability: synthesis and pharmacological evaluation." This evidence was entered into the record by the Examiner in the Final Office Action dated 16 October 2008, at page 8.

4. den Daas *et al.* (1990) Nauyn-Schmiedeberg's Arch. Pharmacol., 343:665-659. This evidence was entered into the record by the Examiner in the Final Office Action dated 16 October 2008, at page 5.

5. Hacksell *et al.* (1979) J. Med. Chem. 22(12):1469–1475. This evidence was entered into the record by the Appellant in the Information Disclosure Statement dated 15 April 2008.

6. Swart *et al.* (1993) Toxicol. Meth. 3:279–290. This evidence was entered into the record by the Appellant in the Information Disclosure Statement dated 15 April 2008.

(J) RELATED PROCEEDINGS APPENDIX (37 C.F.R. 41.37(c)(1)(x))

None.